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Docket No.: PF-0339-2 CPA

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1646

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Bandman et al.

Title:	NEW HUMAN INTEGRAL MEMBRANE PROTEIN		
Serial No.:	09/265,710	Filing Date:	March 9, 1999
Examiner:	Ulm, J.D.	Group Art Unit:	1646

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REPLY BRIEF ON APPEAL

Sir:

I. INTRODUCTION

This is Appellants' Reply Brief on Appeal (submitted in triplicate) in response to the Examiner's Answer dated December 2, 2002 ("the Examiner's Answer") in the above-identified application (the Bandman '710 application).

On page 3 of the Examiner's Answer the Examiner asserts that the Brief on Appeal of August 29, 2002, is deficient because the Brief contains the statement that the "polypeptides of the present invention are useful, for example for toxicology testing, drug discovery, and disease diagnosis" (Examiner's Answer, page 3 at ¶ 5). These utilities are the subject of the Appeal. Appellants disagree with the Examiner's position, and address this issue in § II below.

On page 3 of the Examiner's Answer the Examiner states that "the rejection of claims 1, 2, 12, 21, 42 to 45 and 48 to 51 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof" (Examiner's Answer, page 3 at ¶ 7). The claims stand or fall together only with respect to issues 1 and 2. With respect to issue 3, only claims 2, 21, 42, 44, 45, 48, 50, and 51 are grouped together for purposes of the Appeal, as indicated in the Brief on Appeal of August 29, 2002 (at page 4, § (8)), and as indicated by the Examiner at, for example, page 5, § 6.

In addition, in the Examiner's Answer the Patent Examiner:

(1) maintained the rejection of the claims on appeal under 35 U.S.C. § 101 on the grounds that the claimed polypeptides are allegedly not supported by a specific and substantial credible utility,

(2) maintained the rejection of the claims on appeal under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement because of the invention's alleged lack of utility, and

(3) maintained the rejection of claims 2, 27, 30, and 34, on appeal, under 35 U.S.C. § 112, first paragraph, for alleged lack of written description/possession of the claimed polypeptide "variants."

II. ISSUES 1 & 2 -- UTILITY REJECTIONS

A. Overview of Utility Rejections

In the rejections of the claimed invention for alleged lack of utility, the Examiner does not disprove the following:

1) that the claimed NIMPH polypeptide having the amino acid sequence of SEQ ID NO:1 is expressed in humans; and

2) that all, or almost all, proteins expressed in humans have specific and substantial utility for measuring undesired side effects of drug candidates in toxicological testing.

It follows that the claimed invention is, by **more** than a reasonable probability, useful. There is no dispute that the Appellants need show no more than a reasonable probability that the claimed invention is useful to meet the requirements of 35 U.S.C. § 101 and § 112, first paragraph.

The Examiner never assails or even addresses this compelling logic. The Examiner continues to insist that the Appellants prove not only reasonable probability of utility, **but also** the biological or physical function of the claimed invention.

Nothing in the law requires the Appellants to prove biological function, and the Examiner does not point to anything in the law suggesting such a requirement. Indeed, the only law on this point is to the contrary: it is settled law -- and the Examiner does not rebut this -- that how an invention works (that is, its function) is utterly irrelevant to the utility analysis. In short, the entirety of the Examiner's argument is based on the confusion between, and improper equation of, use and function.

The Examiner apparently would rely on *In re Kirk* for the proposition that the Appellants must demonstrate biological function. *Kirk* requires no such thing. Indeed, *Kirk* is completely consistent with the requirement that the Appellants need only show utility of the claimed invention to reasonable probability. In *Kirk*, the applicant could not show reasonable probability because the only fact alleged by the applicant was that the claimed invention is a steroid. Because so many steroids -- indeed most of them -- have absolutely no use whatsoever, it followed that the applicant had not shown a reasonable probability of utility.

Application of the same logic to this case -- which the Examiner refuses to do -- yields a completely different result. In this case, the Appellants have identified the claimed invention as a member of a much better defined and narrower group: proteins expressed in humans. As demonstrated above, because proteins expressed in humans are predominantly useful, the Appellants can state with great confidence that the claimed invention is useful. How the invention actually works is utterly irrelevant to the analysis.

B. Responses to Specific Arguments by the Examiner

1. The Examiner states on page 5 of the Examiner's Answer that "[i]n the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it" (emphasis in original). The Examiner confuses function with use. These are not synonymous. Knowledge of the natural ligands of NIMPH or of its biological significance is irrelevant. It is the utility of the integral membrane proteins, not their biological functions, that can be imputed to the claimed polypeptides. The point for the purposes of the utility standard is that NIMPH,

as an integral membrane protein expressed in humans, is indeed useful for toxicology testing, drug discovery, and disease diagnosis.

The Examiner continues his argument by stating that "[t]o employ a protein of the instant invention in the identification of substances which inhibit or induce its activity is clearly to use it as the object of further research" (Examiner's Answer, page 5). With respect to the utility of the claimed polypeptides in toxicology testing, the Examiner is wrong. In toxicology testing, the claimed polypeptides are not the object of the research. The claimed polypeptides are a research tool used to assess the toxicity of drug candidates which are specifically targeted to **other** polypeptides. It is the other polypeptides and the drug candidates which are the object of the research.

2. The Examiner contends on page 8 of the Examiner's Answer that "toxicology testing and drug discovery are not specifically recited in the specification as originally filed." The Examiner's argument amounts to nothing more than the Examiner's disagreement with the Furness Declaration and the Appellants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Examiner's own judgment for that of the Appellants' expert. The Examiner must accept the Appellants' assertions to be true. The Examiner is, moreover, wrong on the facts because the Furness Declaration demonstrates how one of skill in the art, reading the specification at the time the parent of the Bandman '710 application was filed (July 14, 1997), would have understood that specification to disclose the use of SEQ ID NO:1 in protein expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the Furness Declaration at, e.g., ¶¶ 10-13).

Regardless, toxicology testing was recited in the specification as originally filed. For example, the specification recites that "[t]herapeutic efficacy and **toxicity** may be determined by standard pharmaceutical procedures" (page 33, lines 29-30; emphasis added). Also, the specification recites that polynucleotides which encode the claimed polypeptides can be included on a microarray that "can be used to monitor the expression level of large numbers of genes," and this information may be used "in developing and monitoring the activity of therapeutic agents" (page 38, lines 24-30).

3. On page 9 of the Examiner's Answer, the Examiner states that "Appellant has failed to identify the consequences of identifying a compound which is toxic to the claimed polypeptide," and that "Appellant has not disclosed the practical benefit of determining the toxic (denaturing)

concentration of a compound . . ." Mr. Furness in his Declaration states, and one of skill in the art would know, that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets" (Furness Declaration, ¶ 10 at page 8). Thus, if the expression of a particular polypeptide or polynucleotide is affected in any way by exposure to a test compound, and if that particular polypeptide or polynucleotide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polypeptide sequence and its associated polynucleotide sequence.

Therefore, the "consequences of identifying" a toxic compound, and the "practical benefit of determining the toxic . . . concentration" of a compound, is the shortening of the drug development process. For example, Rockett et al. (Xenobiotica, 1999, 29:655-656; of record) state that knowledge of the toxicity of a drug candidate results in "shortening the development process and contributing substantially to the safety assessment of new drugs" (see, e.g., page 11 of the Brief on Appeal of August 29, 2002).

4. The Examiner argues on page 9, and again on page 10, that use as a control for toxicology testing is not specific, substantial, and credible, and therefore not well-established, because it "is a general utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA" (Examiner's Answer, page 9). The Examiner doesn't point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of proteins or DNA can be so used, then they all have utility. The issue is, once again, whether the claimed invention has any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of "well established" utilities **presupposes** that many different inventions can have the exact same utility. If the Examiner's argument was correct, there could never be a well established utility, because you could always find a generic group with the same utility!

Furthermore, the Examiner is factually incorrect in stating that any collection of proteins or DNA could be used as controls for toxicology testing. The property of NIMPH that makes it useful as

a control for toxicology testing is its expression in naturally occurring cells. A protein or DNA molecule having a non-naturally occurring random sequence would most likely not be useful as a control for toxicology testing.

5. On page 10, the Examiner asserts that the claimed polypeptide has no well-established use in drug development, toxicology studies, or disease diagnosis because "[t]he artisan is required to perform substantial further experimentation on the claimed material itself in order to determine to what 'practical use' any expression information regarding this 'isolated' polypeptide could be put." Not so. The claimed polypeptide can be used for toxicology testing in drug discovery without any knowledge of its disease association or biological function. Monitoring the expression of the claimed polypeptide gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polypeptide, regardless of the disease association or biological function of the claimed polypeptide. The claimed polypeptide is useful for measuring the toxicity of drug candidates specifically targeted to **other** polypeptides, regardless of any possible utility for measuring properties of the claimed polypeptide itself.

6. On page 10 of the Examiner's Answer, the Examiner again insists that "toxicology testing is not a substantial and specific utility" because "all human proteins can be employed in such a process irrespective of their normal function." Furthermore, the Examiner states that using a polypeptide in toxicology testing is analogous to employing it "as a molecular weight marker, which is neither a specific or substantial utility" (Examiner's Answer, page 10). The Examiner continues to ignore the utility of the claimed polypeptide for measuring the toxicity of drug candidates specifically targeted to polypeptides **other than** the claimed polypeptide (see §§ II.B.1 and II.B.5, above). Such a utility is specific and substantial because the effect of any particular drug candidate on the expression of the claimed polypeptide differs from the effect of that drug candidate on any other naturally occurring polypeptide, and also differs from the effect of any other drug candidate on the expression of the claimed polypeptide.

The Examiner further contends that the asserted utility of the claimed polypeptide in toxicology testing "is neither a specific or substantial utility" because that "would be comparable to conceding that any object of fixed mass has *prima facie* utility as a weight standard, irrespective of any other properties possessed by that object" (Examiner's Answer, pages 10-11). This is an inaccurate

analogy. For utility as a weight standard, an object need only have the property of having a fixed mass. Any object having that same fixed mass could be used in place of that weight standard. The results of using any weight standard having that one particular property (i.e., a particular fixed mass) would be the same. For utility in toxicology testing, every distinct polypeptide expressed in humans **does** have utility based solely on the property of being expressed in humans. However, the results obtained from using any particular human-expressed polypeptide in toxicology testing is **specific to both the compound being tested and the polypeptide used in the test**. No two human-expressed polypeptides are interchangeable for toxicology testing because the effects on the expression of any two such polypeptides will differ depending on the identity of the compound tested and the identities of the two polypeptides. Therefore, the asserted utility of the claimed polypeptide for toxicology testing is specific and substantial, and more than adequately satisfies the statutory requirements for utility.

7. The Examiner insists that the Declaration of Mr. Furness is "insufficient to overcome the rejection . . . because it merely presents Applicant's arguments of record in declaratory form" (Examiner's Answer, pages 12-13). This is improper. Contrary to the Examiner's assertion, a declaration or affidavit by an expert witness is not equivalent to arguments made by Appellants' representative; such a declaration or affidavit is considered to be objective evidence. Regarding declarations which provide evidence traversing rejections, the M.P.E.P. states that "[t]he arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)." M.P.E.P. § 716.01(c).

The policy of the Patent Office in considering affidavits or declarations traversing rejections is that "[e]vidence traversing rejections **must** be considered whenever present." M.P.E.P. § 716.01 (emphasis added). As such, the Examiner's refusal to give full consideration to the substance of the Furness Declaration is improper. "Where the evidence is insufficient to overcome the rejection, the examiner must specifically explain why the evidence is insufficient. General statements . . . without an explanation supporting such findings are insufficient." *Id.* The Examiner's statement that the Furness Declaration "merely presents Applicant's arguments of record in declaratory form" is just such a general statement, and does not meet the requirement to **specifically explain why** Mr. Furness' Declaration is allegedly insufficient to overcome the Examiner's utility rejection. For at least this reason, the rejections under 35 U.S.C. § 101 and § 112, first paragraph, should be overturned.

C. Summary

It is true that just about any expressed protein will have use as a toxicology control, but Appellants need not argue this for the purposes of this case. Appellants argue only that this particular claimed invention could be so used, and have provided the Declaration of Furness to back this up. The Examiner is completely wrong to characterize Appellants' argument re: utility of a polypeptide as a toxicology control somehow requires the person using the invention to do further research to identify the biological function of that polypeptide. The point is not whether the invention is, in any given toxicology test, differentially expressed. The point is that the invention provides a useful measuring stick regardless of whether there is or is not differential expression. That makes the invention useful today, in the real world, for real purposes having nothing to do with further characterization of the invention itself.

III. ISSUE 3 -- WRITTEN DESCRIPTION REJECTIONS

A. Overview of Written Description Rejections

Nowhere in the Examiner's Answer does the Examiner offer any evidence that one of ordinary skill in the art would not have understood, from the disclosure in the specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art," that Appellants were in possession of the claimed polypeptide variants. The Examiner instead states that "[t]he only composition which is described in the instant specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed composition was an isolated DNA encoding a single protein having the amino acid sequence presented in SEQ ID NO:1" (Examiner's Answer, page 6), and that "the instant specification does not describe that structural feature or combination of features which distinguishes a polypeptide which meets both of these limitations ['having at least 90% amino acid identity to SEQ ID NO:1' and 'naturally occurring'] from a polypeptide which meets only the first limitation" (Examiner's Answer, page 13).

The Examiner's position is contrary to the Patent and Trademark Office's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]** (emphasis added)

Here, there simply is no requirement that the claims recite the sequences of particular variants because the claims already provide sufficient structural definition of the claimed subject matter. That is, the claimed variants are defined in terms of SEQ ID NO:1. Because the claimed variants are defined in terms of SEQ ID NO:1, the precise chemical structure of every variant within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention.

B. <u>Responses to Specific Arguments by the Examiner</u>

1. On page 7 of the Examiner's Answer, the Examiner states that "the instant specification does not provide a written description of any other isolated nucleic acid or protein and certainly not the very broad genus of protein encompassed by the term 'comprising' 'a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1' or 'comprising' 'a fragment thereof'." Appellants respectfully point out that, with respect to polypeptide fragments of the invention, the claims recite "an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1." The Examiner has not presented any specific arguments to support a rejection of the recited immunogenic fragments for lack of written description under 35 U.S.C. § 112, first paragraph.

2. On page 7, the Examiner seems to imply that the use of the transitional phrase "comprising" results in an overly broad claim, and would require that the specification provide a written description of any possible element which could be a part of, but is not essential to, the claimed subject matter. The

transitional phrase " '[c]omprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." M.P.E.P. § 2111.03. The specification has described numerous examples of polypeptides "comprising" the recited variants of SEQ ID NO:1, such as fusion proteins and coupled proteins (Specification, e.g., at page 17, lines 18-24; and page 24, lines 7-26). One of skill in the art would understand that Appellants had possession of the described polypeptides, "comprising" the recited variants of SEQ ID NO:1, without an explicit disclosure of every possible element which could be a part of, but is not essential to, the claimed subject matter.

3. The Examiner, on page 8, insists that the skilled artisan cannot determine if a polypeptide "meets the 'naturally occurring' limitation of the instant claims." As the Examiner recognizes, the specification discloses that "the instant claims are intended to encompass 'substantially purified NIMPH obtained from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably human, from any source whether natural, synthetic, semi-synthetic, or recombinant'." (Examiner's Answer, page 6). The specification also discloses that the term "amino acid sequence" includes polypeptides which are "naturally occurring" molecules (e.g., at page 6, lines 16-22). Based on these disclosures, one of skill in the art would reasonably conclude that the Appellants were in possession of a "naturally occurring polypeptide having at least 90% amino acid identity to SEQ ID NO:1" at the time the application was filed.

Furthermore, the Examiner asserts that a skilled artisan would not be able to distinguish a polypeptide which meets the "at least 90% amino acid identity to SEQ ID NO:1" limitation from a polypeptide which meets both this former limitation and the "naturally occurring" limitation (e.g., at page 8 and page 13 of the Examiner's Answer). The Examiner bases this assertion on a citation to the M.P.E.P. at § 2163 which states that "even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA" (Examiner's Answer, pages 7-8). This citation is not germane to the claims at issue because the citation refers to a "biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence." M.P.E.P. § 2163.

In contrast, the claims at issue define the claimed polypeptides by structural characteristics. By the Patent Office's own guidelines, the written description requirement can be satisfied by "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or** some combination of such characteristics" (P.T.O. Guidelines, *supra*; emphasis added). Thus, "complete or partial structure," such as the structural definition of the claimed polypeptides based on at least 90% sequence identity to SEQ ID NO:1, is enough to provide an adequate written description of the claimed invention.

C. Summary

The Examiner has asserted that the sequences of the claimed polypeptide variants must be provided in order for there to be an adequate written description of the claimed genus. However, this is not true. The P.T.O. Guidelines state that an adequate written description can be provided by "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or** some combination of such characteristics" (P.T.O. Guidelines, *supra*; emphasis added). Therefore, there is no absolute requirement to provide the sequence of every claimed polypeptide. The claimed polypeptide variants have been described by chemical structure (e.g., in terms of SEQ ID NO:1) in conjunction with physical properties (e.g., occurrence in nature). Therefore, the written description requirement has been met.

For at least the above reasons and the reasons presented in the Brief on Appeal, reversal of this rejection is requested.

IV. CONCLUSION

For all the foregoing reasons and the reasons stated in the Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This form is enclosed in triplicate.

Respectfully submitted,
INCYTE GENOMICS, INC.

Date: Jan. 27, 2003.

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